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# Copper-catalyzed synthesis of 2-imidazolines and their *N*-hydroxyethyl derivatives under various conditions

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ABSTRACT

A rapid and efficient method for the synthesis of 2-imidazolines and their *N*-hydroxyethyl derivatives from the reaction of aromatic nitriles with ethylenediamine (EDA) or *N*-(2-aminoethyl)ethanolamine (AEEA) using cupric indole-3-acetate (Cu(II)–$(IAA)_2$) as a reusable catalyst under reflux and microwave conditions is reported. And seven new *N*-hydroxyethyl-imidazolines were reported for the first time.



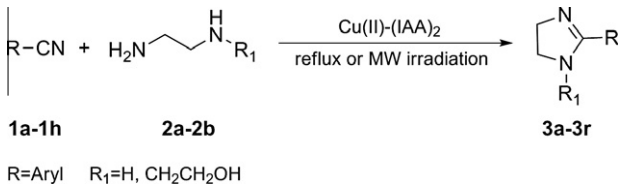
Imidazolines and their derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals.[1] They exhibit significant activity against several diseases including hyperglycaemia,[2] inflammation,[3] hypertension,[4] hypercholesterolemia[5] and cancer.[6] Moreover, some imidazoline derivatives have been demonstrated to be imidazoline receptors,[7] phase transfer catalysts[8] and synthetic intermediates.[9] They can also act as ligands coordinated to transition metals for asymmetric catalysis.[10]

A number of methods have been developed for the synthesis of imidazolines and their derivatives from carboxylic acids,[11] esters,[12] nitriles,[13] orthoesters,[14] hydroximoylchlorides[15] and hydroxyamides.[16] However, there are some disadvantages in these methods such as long reaction time, high temperature, tedious work-up, corrosive reagents and large amounts of toxic solid supports. Thus, an efficient, simple and environmentally friendly synthesis method is worthwhile endeavour. In this context, direct access of imidazolines by the utilization of diamines and nitriles has attracted significant attention from academic community. Due to usage of Lewis acids as catalysts, the reaction becomes efficient, environmentally friendly and economical. Until now, many ordinary Lewis acids have been reported as catalysts such as $ZrOCl_2{\cdot}8H_2O$,[17] supported 12-tungstophosphoric acid[18] 1,3-dibromo-5,5-dimethylhydantoin,[19] thioacetamide.[20] Since copper was first used as a catalyst in synthesis chemistry in 1901,[21] copper-catalyzed reactions have received considerable attentions because of their efficiency and low cost.[22] However, as far as we know, only CuCl had been used as a catalyst by Rousselet and it was not efficient enough in the preparation of imidazolines.[23] The catalytic activity of copper has not been fully explored in this reaction.

Indole-3-acetic acid (IAA) is a substance with essential and multifunctional biological significance,[24] and the metal complexes of IAA have been reported recently.[25] But to the best of our knowledge, there are no reports on direct use of the metal complexes of IAA as a heterogeneous catalyst in organic reaction, especially in the synthesis of imidazolines.

In consequence, we explored the capability of cupric indole-3-acetate as an efficient and reusable heterogeneous catalyst for the synthesis of imidazolines and their *N*-hydroxyethyl derivatives from the reaction of aromatic nitriles and EDA or AEEA under either reflux conditions or under microwave irradiation (Scheme 1).

In order to identify the optimal reaction conditions for the reaction, a number of copper catalysts were examined in the reaction of EDA with 3-cyanopyridine under reflux condition for 4 h firstly. Unexpectedly, only Cu(II)–$(IAA)_2$[26] showed extraordinary reaction




**Scheme 1.** Preparation of 2-imidazolines and *N*-hydroxyethyl derivatives from nitriles and diamines.

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**Table 1**
Effect of various copper salts on the reaction of 3-cyanopyridine with EDA[a]

| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | Cupric chloride | 61 |
| 2 | Cupric nitrate | 52 |
| 3 | Cupric sulfate | 9 |
| 4 | Cupric benzoate | 73 |
| 5 | Cupric nicotinate | 25 |
| 6 | Cupric isonicotinate | 79 |
| 7 | Cupric 4-chlorobenzoate | 4 |
| 8 | Cupric oxalate | 22 |
| 9 | Cupric malonate | 20 |
| 10 | Cupric cinnamate | 38 |
| 11 | Cupric 2-aminobenzoate | 28 |
| 12 | Cupric 1-naphthoate | 45 |
| 13 | Cupric phthalate | 3 |
| 14 | Cupric 4-nitrobenzoate | 27 |
| 15 | Cupric 4-metoxybenzoate | 71 |
| 16 | Cupric 4-hydroxybenzoate | 25 |
| 17 | La(III)–$(IAA)_3$ | 1 |
| 18 | Zn(II)–$(IAA)_2$ | 2 |
| 19 | Sm(III)–$(IAA)_3$ | 1 |
| 20 | Cu(II)–$(IAA)_2$ | 85 |

[a] All reactions were carried out according to the typical experimental procedure.
[b] Yield determined by GC–MS using an internal standard.

activity for this reaction, but other copper salts such as cupric chloride, cupric nitrate, cupric sulfate, cupric benzoate, cupric nicotinate, cupric isonicotinate, cupric 4-chlorobenzoate, cupric oxalate, cupric malonate, cupric cinnamate, cupric 2-aminobenzoate, cupric 1-naphthoate, cupric phthalate, cupric 4-nitrobenzoate, cupric 4-metoxybenzoate and cupric 4-hydroxybenzoate were either less active or inert as a catalyst. Moreover, the catalytic activity of other metal complexes of indole-3-acetic acid was also investigated, and the yield was not more than 2% (Table 1).

**Table 2**
Solvent effects on the reaction of 3-cyanopyridine with EDA[a]

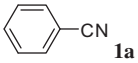
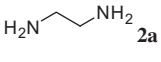
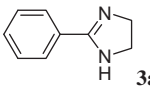
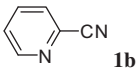
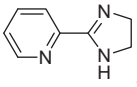
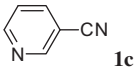
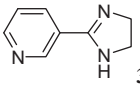
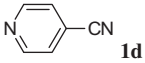
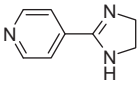
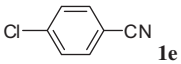
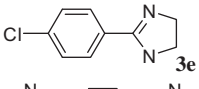
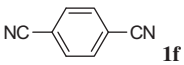
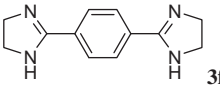
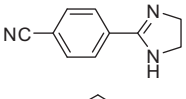
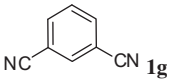
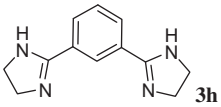
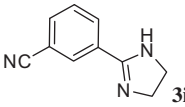
| Entry | Solvents | Temperature (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | None | 116[c] | 4 | 85 |
| 2 | EtOAc | 77 | 4 | 5 |
| 3 | $CH_2Cl_2$ | 40 | 4 | 3 |
| 4 | $CH_3OH$ | 65 | 4 | 41 |
| 5 | $C_2H_5OH$ | 78 | 4 | 22 |
| 6 | DMF | 153 | 4 | 73 |
| 7 | $^{i}$PrOH | 83 | 4 | 3 |

[a] Reaction conditions: 3-cyanopyridine (4.0 mmol), EDA (32 mmol), Cu(II)–$(IAA)_2$ (0.8 mmol).
[b] Yield determined by GC–MS using an internal standard.
[c] The boiling point of EDA.

In continuation of this work, we have used Cu(II)–$(IAA)_2$ as an efficient catalyst to investigate the effect of different solvents under their corresponding reflux temperature for the same reaction as above (Table 2). Thus, optimal conditions were: Cu(II)–$(IAA)_2$ as the catalyst, solvent free and 116 °C (the boiling point of EDA).

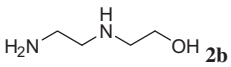
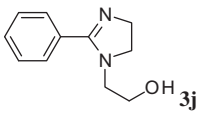
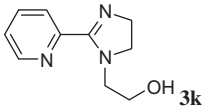
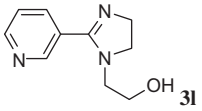
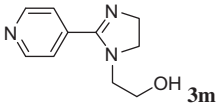
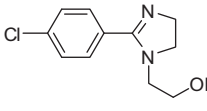
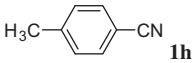
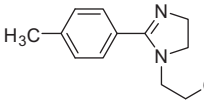
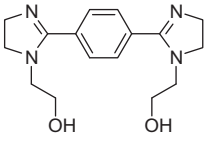
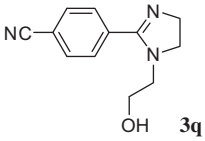
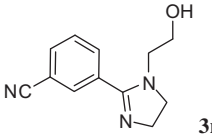
The chosen reflux reaction conditions have been used for the successful preparation of a series of 2-substituted imidazolines.[27]

**Table 3**
Preparation of imidazolines and *N*-hydroxyethyl-imidazolines from aromatic nitriles and diamines under reflux condition[a] and under MW irradiation[b]

| Entry | Nitriles (1) | Diamines (2) | Products (3) | Reflux conditions | | MW irradiation | |
|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield[c] (%) | Time (min) | Yield[c] (%) |
| 1 |  **1a** |  **2a** |  **3a** | 240 | 87 | 5 | 91 |
| 2 |  **1b** | **2a** |  **3b** | 240 | 91 | 5 | 92 |
| 3 |  **1c** | **2a** |  **3c** | 240 | 85 | 5 | 92 |
| 4 |  **1d** | **2a** |  **3d** | 240 | 93 | 5 | 94 |
| 5 |  **1e** | **2a** |  **3e** | 240 | 78 | 5 | 87 |
| 6 |  **1f** | **2a** |  **3f** | 360 | 88 | 20 | 90 |
| 7 | **1f** | **2a** |  **3g** | 120 | 75 | 5 | 80 |
| 8 |  **1g** | **2a** |  **3h** | 360 | 85 | 20 | 89 |
| 9 | **1g** | **2a** |  **3i** | 120 | 70 | 5 | 79 |

(*continued on next page*)

**Table 3** (*continued*)

| Entry | Nitriles (1) | Diamines (2) | Products (3) | Reflux conditions | | MW irradiation | |
|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield[c] (%) | Time (min) | Yield[c] (%) |
| 10 | **1a** |  **2b** |  **3j** | 180 | 85 | 5 | 91 |
| 11 | **1b** | **2b** |  **3k** | 180 | 91 | 5 | 96 |
| 12 | **1c** | **2b** |  **3l** | 180 | 87 | 5 | 92 |
| 13 | **1d** | **2b** |  **3m** | 180 | 92 | 5 | 94 |
| 14 | **1e** | **2b** |  **3n** | 240 | 83 | 5 | 90 |
| 15 |  **1h** | **2b** |  **3o** | 300 | 83 | 5 | 89 |
| 16 | **1f** | **2b** |  **3p** | 300 | 81 | 20 | 85 |
| 17 | **1f** | **2b** |  **3q** | 120 | 89 | 5 | 93 |
| 18 | **1g** | **2b** |  **3r** | 120 | 88 | 5 | 91 |

[a] All reflux reactions were carried out according to the typical experimental procedure.
[b] All MW reactions were carried out at 80 °C, with 1000 W applied power in a 50 mL round-bottom flask with a glass condenser.
[c] Isolated yield.

Various aromatic and heteroaromatic nitriles reacted with EDA to produce the corresponding imidazolines in high to excellent yields. Bis-imidazolines can also be prepared from the same reaction in the presence of Cu(II)–$(IAA)_2$. As shown in Table 3, bis-imidazolines were obtained from dinitriles in 85–88% yields with longer time (6 h). If the reaction time was reduced to 2 h, mono-imidazolines were generated in 70–75% yields. The synthesis of the mono-imidazolines is very meaningful, because the remaining nitrile group can also be converted to other functional groups.

In order to further verify the performance of this catalytic system, we used AEEA instead of EDA to react with various aromatic and heteroaroatic nitriles in the presence of catalytic amounts of Cu(II)–$(IAA)_2$, and the results were satisfactory. To the best of our knowledge, this method of preparation of *N*-hydroxyethyl-imidazolines and bis-*N*-hydroxyethyl-imidazolines from nitriles has not been reported yet. In this way, seven *N*-hydroxyethyl-imidazolines involved in this article are reported for the first time (**3k–n**, **3p–r**[28]).

Previously, it was reported that microwave irradiation could be used as an efficient approach to achieve good yields, short reaction time, and mild reaction conditions. Therefore, we examined the effect of MW irradiation on the synthesis of imidazolines and bis-imidazolines from the reaction of nitriles with EDA in the presence of catalytic amount of Cu(II)–$(IAA)_2$.[29] A variety of nitriles and dinitriles were used for this manner. The corresponding imidazolines and bis-imidazolines were obtained in high yields (81–91%). And *N*-hydroxyethyl-imidazolines can also be synthesized from nitriles and AEEA in high yields (85–93%) in the presence of Cu(II)–$(IAA)_2$ with the assistance of MW irradiation. The results are shown in Table 3.

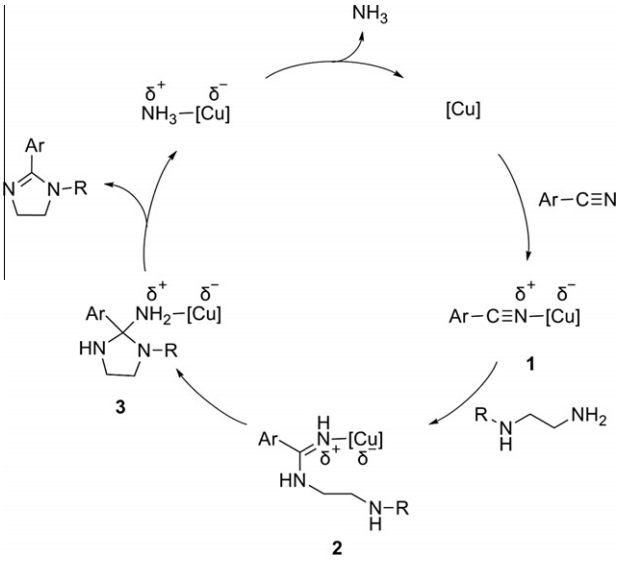
The reusability of catalysts is one of the important benefits for large-scale operations and commercial applications. Therefore, we investigated the reusability of Cu(II)–$(IAA)_2$ catalyst in the reaction of 3-cyanopyridine with EDA. The catalyst can be recovered by simple filtration, washing and drying at 60 °C. Under either reflux conditions or MW irradiation, the catalyst has been consecutively reused five times without significant loss of activity (Table 4).

A plausible mechanism for the reaction has been proposed in Scheme 2. Cu(II)–$(IAA)_2$ first activates the nitrile group by the

**Table 4**
Reusability of Cu(II)–$(IAA)_2$ catalyst in the synthesis of imidazolines

| Recycling no. | Reflux conditions | | MW irradiation | |
|---|---|---|---|---|
| | Time (min) | Yield[a] (%) | Time (min) | Yield[a] (%) |
| 1 | 240 | 97 | 5 | 99 |
| 2 | 240 | 97 | 5 | 99 |
| 3 | 240 | 96 | 5 | 98 |
| 4 | 240 | 94 | 5 | 98 |
| 5 | 240 | 94 | 5 | 97 |

[a] Yield determined by GC–MS using an internal standard.




**Scheme 2.** Proposed mechanism for the synthesis of 2-imidazolines and their *N*-hydroxyethyl derivatives catalyzed by Cu(II)–$(IAA)_2$.

formation of nitrogen cation 1. EDA or AEEA attacks 1 to afford 2 and 3. Finally, the corresponding imidazoline or *N*-hydroxyethyl-imidazoline is produced by releasing $NH_3$ and the catalyst for the next catalytic cycle.

In summary, we have first demonstrated that Cu(II)–$(IAA)_2$ can be used as a green and reusable catalyst for efficient synthesis of imidazolines and their *N*-hydroxyethyl derivatives under either reflux condition or MW irradiation. The attractive features of this procedure are the mild reaction conditions, high conversions, solvent free and reusable catalyst, all of which make it a useful and attractive strategy for the preparation of various imidazolines. In addition, a new method of synthesizing the *N*-hydroxyethyl-imidazolines is proposed and seven *N*-hydroxyethyl-imidazolines are reported for the first time.

## Acknowledgements

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26. The preparation of Cu(II)–$(IAA)_2$. To a solution of indole-3-acetic acid (5.7 mmol, 1.0 g) in 15 mL of water, a solution of NaOH (5.7 mmol, 0.23 g) in 10 mL of water was slowly added under stirring. To this solution, an aqueous solution of $CuCl_2$ (previously prepared with 2.8 mmol $CuCl_2{\cdot}2H_2O$ in 15 mL of water) was added, then green precipitation generated. The precipitation was washed with water and dried under vacuum. The identities of products were confirmed by IR data, IR (KBr): 3381, 1598, 1417, 1282, 794, 743 $cm^{-1}$.
27. The typical reaction procedure under reflux condition. In a 50 mL round bottom flask equipped with a water condenser, magnetic stirrer and oil-bath, a mixture of nitrile (4.0 mmol), EDA (32 mmol) and Cu(II)–$(IAA)_2$ (0.8 mmol) was heated under reflux condition. The progress of the reaction was monitored by TLC (eluent: EtOAc/MeOH, 3:1). After completion of the reaction, $CH_2Cl_2$ (10 mL) was added and the catalyst was filtered. The solvent was evaporated under reduced pressure and the crude products were obtained. Compound **3a–i** were purified by recrystallization from cyclohexane respectively, and **3j–r** were purified by a silica gel column (eluent: EtOAc/MeOH, 3:1). The identities of products were confirmed by mp, $^1H$ NMR, MS and IR data.
28. The characterization of the new compounds. Compound **3k**: Light yellow liquid. IR (KBr): 3372, 2943, 1659, 1532, 1460, 1434, 1052, 750, 692 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 2.90 (m, 2H, $CH_2$), 2.99 (m, 2H, $CH_2$), 3.47 (s, 1H, OH), 3.67 (m, 2H, $CH_2$), 3.72 (m, 2H, $CH_2$), 7.43 (m, 1H, ArH), 7.84 (m, 1H, ArH), 8.17 (d, 1H, ArH), 8.55 (d, 1H, ArH); MS *m/z*: 191 (9.6%), 160 (53.6%), 118 (4.2%), 105 (21.1%), 78 (34.8%), 56 (100%). Compound **3l**: Light yellow liquid. IR (KBr): 3337, 2957, 1607, 1427, 1299, 1057, 749, 707 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 2.52 (s, 1H, OH), 3.37 (m, 2H, $CH_2$), 3.76 (m, 2H, $CH_2$), 4.06 (m, 2H, $CH_2$), 7.44 (m, 1H, ArH), 8.20 (d, 1H, ArH), 8.77 (d, 1H, ArH), 8.97 (s, 1H, ArH); MS *m/z*: 191 (11.4%), 160 (50.1%), 118 (13.0%), 56 (100%). Compound **3m**: Light yellow liquid. IR (KBr): 3349, 2950, 1650, 1549, 1419, 1307, 1062, 839, 752, 683 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 2.51 (s, 1H, OH), 2.83 (m, 2H, $CH_2$), 2.92 (m, 2H, $CH_2$), 3.55 (m, 2H, $CH_2$), 3.73 (m, 2H, $CH_2$), 7.51 (d, 1H, ArH), 7.70 (d, 1H, ArH), 8.65 (d, 1H, ArH), 8.70 (d, 1H, ArH); MS *m/z*: 191 (11.9%), 160 (53.2%), 118 (11.4%), 56 (100%). Compound **3n**: Light yellow solid, mp 137–138 °C. IR (KBr): 3268, 2948, 1638, 1597, 1487, 1447, 1321, 1093, 1013, 843, 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 3.04 (m, 2H, $CH_2$), 3.17 (m, 2H, $CH_2$), 3.84 (s, 1H, OH), 3.99 (m, 2H, $CH_2$), 4.18 (m, 2H, $CH_2$), 7.37 (d, 1H, ArH), 7.43 (d, 1H, ArH), 7.85 (d, 1H, ArH), 7.95 (d, 1H, ArH); MS *m/z*: 226 (2.9%), 224 (9.0%), 193 (34.3%), 56 (100%). Compound **3p**: White solid, mp 249–250 °C. IR (KBr): 3133, 2874, 2833, 1594, 1523, 1424, 1264, 1247, 1088, 859, 688 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$: 2.60 (m, 4H, $CH_2$), 2.69 (m, 4H, $CH_2$), 3.50 (m, 4H, $CH_2$), 3.75 (m, 4H, $CH_2$), 4.82 (s, 2H, OH), 7.60 (m, 4H, ArH); MS *m/z*: 303[M+1$^+$]. Compound **3q**: White solid, mp 162–163 °C. IR (KBr): 3157, 2879, 2834, 2227, 1590, 1553, 1431, 1363, 1251, 1064, 869, 848, 745 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 2.19 (s, 1H, OH), 3.22 (m, 2H, $CH_2$), 3.63 (m, 2H, $CH_2$), 3.77 (m, 2H, $CH_2$), 3.96 (m, 2H, $CH_2$), 7.72 (d, 2H, ArH), 7.80 (d, 1H, ArH); MS *m/z*: 215 (8.8%), 184 (34.4%), 142 (8.8%), 102 (8.3%), 56 (100%). Compound **3r**: White solid, mp 120–121 °C. IR (KBr): 3141, 2901, 2230, 1613, 1588, 1495, 1430, 1362, 1256, 1093, 807, 706; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 2.33 (s, 1H, OH), 3.20 (m, 2H, $CH_2$), 3.59 (m, 2H, $CH_2$), 3.75 (m, 2H, $CH_2$), 3.96 (m, 2H, $CH_2$), 7.54 (m, 1H, ArH), 7.72 (d, 1H, ArH), 7.89 (d, 1H, ArH), 7.97 (s, 1H, ArH); MS *m/z*: 215 (8.9%), 184 (35.2%), 142 (8.5%), 102 (7.8%), 56 (100%).

29. The typical reaction procedure under MW irradiation. A mixture of nitrile (10 mmol), EDA (40 mmol) and Cu(II)–$(IAA)_2$ (2.0 mmol) was irradiated with microwave (1000 W) for 5–20 min by pulsed irradiation. At the end of the reaction (monitored by TLC, eluent: EtOAc/MeOH, 3:1), the mixture was cooled to room temperature, $CH_2Cl_2$ was then added and the catalyst was filtered. Evaporation of the solvent gave the almost pure product. Further purification was performed as for the procedure used in the synthesis of imidazolines under reflux condition. The identities of products were confirmed by mp, $^1H$ NMR, MS and IR data.